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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/664,444	09/18/2000	John C Bell	18003	4773

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/664,444	BELL ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,19 and 24-63* is/are pending in the application.

4a) Of the above claim(s) *2-4,14-17 and 38-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-13,19 and 24-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-22-2005 and 4-6-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed on 11-26-2004 is acknowledged. Claims 1-17, 19 and 24-63 are pending. Claims 2-4, 14-17 and 38-63 remain withdrawn from consideration as being drawn to non-elected inventions. Claims 1, 5-13, 19 and 24-37 are currently under examination.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The instant claims are drawn to methods of reducing the viability of hematopoietic tumor cells by administering a virus and optionally interferon.

The rejection of claims 1, 5-13, 19 and 24-37 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record.

As set forth in the previous Office action, the specification, while being enabling for methods utilizing **VSV** for reducing the viability of mylogenous leukemia cell lines *in vitro*, does not provide enablement for the utilization of **VSV** for the reduction of viability of all hematopoietic tumor cells (either *in* vivo or *in vitro*). The specification does not enable any person of skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Applicant argues:

1. The Office has improperly sought to place on Applicant the burden of proving that the invention works.

2. Applicant is not required to submit experimental results demonstrating the anti-tumor activity of VSV. Rather the Office must establish what the specification does not meet the enablement requirement.

3. No evidence or reasoning has bee cited in support of the rejection.

4. In addition to the specification, other sources support the claim that hemapoietic cancers are appropriate targets for VSV therapy.

5. Six different classes of **hemapoietic cell lines** were tested both *in vitro* and *in vivo*

6. All or virtually all hemapoietic tumor cell types are susceptible to the anti-tumor effects of VSV hence there is no need for the specification to disclose which "are susceptible".

7. The Office has improperly tried to place on Applicant the burden of proving *in vivo* efficacy.

8. Cell lines implanted into athymic mice are not only an acceptable model but also a standard by industry and the NCI for determining efficacy of a novel anticancer agent.

9. The FDA accepts positive tumor xenograft results as a sufficient level of preclinical activity when approving a clinical trial for an investigational new drug.

10. Since all five mutants disclosed in the specification (Example 20) were found to be selective at *in vitro* killing of tumor cells the *in vivo* testing of only two of them (Example 25) does not undermine the predictability of *in vivo* efficacy.

11. The Office is exceeding its mandate conferred by the patent laws when requiring Applicant to demonstrate that their invention "provides benefit".

12. The Office cites several references that merely demonstrate that the *in vivo* environment cannot be duplicated *in vitro*. However, *in vitro* experiments continue to be relied upon to identify treatments for *in vivo* use.

12a. The McCormick and Pecora references are cited to demonstrate the ability to correlate *in vitro* results with *in vivo* efficacy.

13. The *in vivo* activity of VSV has been demonstrated (Table A of response).

14. The Office improperly sought to place on Applicant the burden of explaining the mechanism by which the invention works.

15. Toxicity and efficacy are very different and independent endpoints. The lack of toxicity does not imply that there would be a lack of efficacy.

16. The results disclosed in the references cited in Table C of the response confirm the efficacy of VSV when given intravenously to solid tumors in mice.

17. The specification contains *in vivo* data demonstrating the efficacy of intravenous VSV in treating human melanoma xenografts in nude mice.

Applicant's arguments have been fully considered and deemed non-persuasive.

On the basis of experimentation performed using an animal model, the specification asserts the invention can be used to treat cancer. The problem with accepting such an assertion lies in the fact that the data generated using such mouse models cannot be reasonably extrapolated to reliably and accurately predict whether the claimed invention can be used to attenuate at least a substantial number of pathoangiogenic conditions comprising cancer and furthermore, as of yet, the clinical, therapeutic application of cancer "vaccines" to attenuate

cancer has been met with very little success. In addition to references cited in preceding Office actions, which also describe such disappointing results and attribute the lack of success to various differences, such as the poor extrapolation of promising preclinical data to predict clinical efficacy, Wang et al. (*Exp. Opin. Biol. Ther.* 2001; 1 (2): 277-290) reviews the state of the art of T-cell-directed cancer vaccines for treatment of melanoma and states:

> Saved for scattered reports, however, the success of these approaches has been limited and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunization can be induced but is not sufficient, in most cases, to induce tumour regression (abstract).

Wang et al. further states:

> Among the questions raised by this paradoxical observation [that systemic T-cell responses to vaccines often do not lead to objective clinical tumor regression] stands the enigma of whether tumour resistance to immunotherapy is due to insufficient immune response or because tumour cells rapidly adapt to immune pressure by switching into less immunogenic phenotypes [citations omitted].

In addition, Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need

to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Moreover, as noted in preceding Office action, Gura (of record) teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

With further regard to the predictive value of various different preclinical models, Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 2003 Sep 15; 9: 4227-4239) reports in a retrospective analysis that mouse allograft models were not predictive and xenograft models were only predictive for non-small cell lung and ovarian cancers, but not for breast or colon cancers; see entire document (e.g., the abstract).

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials

have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Applicant has argued that the use of xenografts in mice for evaluating therapeutic efficacy of drugs for treating humans is well established; agreeably the model has been utilized, but its use should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation because of the poor extrapolation of the results to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen. Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer.* 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

The position of the Office is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

With regard to Points 1-2 and 7, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as

originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). **The MPEP further states that physiological activity can be considered inherently unpredictable.** Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled.

With regard to Point 3, multiple references were (are) cited in support of the Office's positions (see above and below).

With regard to Points 4, the cited references may disclose that hemapoietic cancers may be an attractive target for VSV, the do not provide support for the *in vivo* treatment of said cancers in any animal other than a mouse.

With regard to Points 5 and 8, the ability to treat cell lines *in vitro* and xenografts *in vivo* (in mice) does not correlate to efficacy for the *in vivo* treatment of carcinomas in any animal other than a mouse (see above).

With regard to Point 6, Applicant has provided no evidence that **all hemapoietic cell types** are susceptible to the anti-tumor effects VSV.

With regard to Point 9, while the FDA may rely on xenograft results to determining whether to approve a clinical trial, it is the clinical trials that determines whether a given treatment modality has efficacy *in vivo*. As outlined above, many treatment modalities that have been effective against xenografts proved to have no efficacy *in vivo*.

With regard to Point 10, even if all five mutants were shown to have efficacy against xenografts in mice that doesn't correlate to *in vivo* efficacy against all hemapoietic cancers nor does it correlate to *in vivo* efficacy in any animal other than a mouse.

With regard to Point 11, enablement of treatment methods requires a demonstration of efficacy that correlates to demonstration of "providing a benefit".

With regard to Point 12, the cited references not only demonstrate that the *in vivo* environment cannot be duplicated *in vitro*, said references also demonstrate that limitations of xenograft based models and the lack of correlation between the efficacy in said models and *in vivo* efficacy in animals other than a mouse.

With regard to Point 13, since neither McCormick nor Pecora utilize VSV to treat hemapoietic cancers, they cannot be relied upon to "demonstrate" that *in vitro* data correlates with *in vivo* efficacy. As outlined above, many treatment modalities that have been effective against xenografts proved to have no efficacy *in vivo*.

With regard to Point 14, Applicant has demonstrated the efficacy of treating xenografts with VSV in mice; this does not correlate to *in vivo* efficacy for the treatment of all carcinomas in all animals (including man).

With regard to Point 15, Applicant is not required to explain the mechanism of action with regard to the anti-tumor effect of VSV. The lack of disclosure with regard to the receptors used by VSV was pointed out to illustrate that one would not know what cell types VSV could infect thus contributing the unpredictability of the claimed invention.

With regard to Point 16, while the lack of toxicity does not imply there would be a lack of efficacy, high toxicity (i.e. lethal toxicity) is indicative of a lack of efficacy (as is the case with the intravenous administration of VSV to PKR-/- mice.

With regard to Points 17 and 18, while the results disclosed in the specification and the references cited in Table C may demonstrate the ability of VSV, when administered intravenously, to treat injected cell lines and xenografts in mice, such data does not correlate to correlate to *in vivo* efficacy for the treatment of all hemapoietic cancers in all animals (including man).

Consequently, as outlined in the previous Office action, the specification, while being enabling for methods utilizing **VSV** for reducing the viability of mylogenous leukemia cell lines *in vitro*, does not provide enablement for the utilization of **VSV** for the reduction of viability of all hematopoietic tumor cells (either *in* vivo or *in vitro*). The specification does not enable any person of skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1, 5-13, 19 and 24-37 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for reasons of record.

The rejection of claims 1 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "administering to the tumor cell a virus" is maintained for reasons of record.

Applicant argues:

1. The limitation of "directly" does not appear in the claim and is being improperly read into the claim by the Examiner.

2. Both direct and indirect administration are encompassed by the scope of the claim and there is no need to characterize what is meant by either term.

Applicant's arguments have been fully considered and deemed non-persuasive.

It is still unclear what is meant by said phrase. Claim 1 recites the phrase "administering to **the** tumor cell **a** virus... It is unclear how this is accomplished when said cell resides (and circulates) within an individual. Moreover, the phrase "to the" can only interpreted as meaning "directly to", therefore, contrary to Applicant's assertion, the Examiner is not improperly reading limitations into the claim.

The rejection of claims 24 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "administering interferon to the tumor cell" is maintained for reasons of record.

Applicant argues:

1. The limitation of "directly" does not appear in the claim and is being improperly read into the claim by the Examiner.

2. Both direct and indirect administration are encompassed by the scope of the claim and there is no need to characterize what is meant by either term.

Applicant's arguments have been fully considered and deemed non-persuasive.

It is still unclear what is meant by said phrase. Claim 24 recites the phrase "administering interferon to **the** tumor cell…". It is unclear how this is accomplished when said cell resides (and circulates) within an individual. Moreover, the phrase "to the" can only interpreted as meaning "directly to", therefore, contrary to Applicant's assertion, the Examiner is not improperly reading limitations into the claim.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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ROBERT A. ZEMAN
PRIMARY EXAMINER

January 31, 2007